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Attorney Docket	STAN-190
First Named Inventor	D. Zeng
Application Number	09/844,544
Filing Date	April 27, 2001
Group Art Unit	1644
Examiner Name	M. Dibrino
Title: *Methods for Inhibition of Polyclonal B Cell and Immunoglobulin Class Switching to Pathogenic Autoantibodies by Blocking CD1-Mediated Interactions*	

Commissioner for Patents
Alexandria, VA 22313

REPLY BRIEF

Appellants have the following remarks in response to the Examiner's Answer of May 9, 2005. No new grounds of rejection have been raised.

ARGUMENT

CLAIMS 1-2, 6-8, 10 AND 12 ARE PATENTABLE UNDER 35 U.S.C. 103(A) OVER AMANO *ET AL.* IN VIEW OF KOTZIN *ET AL.*, ZENG *ET AL.*, BLUMBERG *ET AL.* AND HUGHES.

Appellants respectfully submit that the presently claimed invention is not made obvious by the cited prior art.

The Examiner's Answer states that "it would have been prima facie obvious to one of skill in the art at the time the invention was made to have used the anti-CD1d mAb taught by Zeng *et al.* or Amano *et al.* or the anti-CD1a, b, c and d antibodies taught by Blumberg *et al.* to block CD1 recognition by T cells as taught by Amano *et al.* by administration of antibodies to subjects with SLE, and hence to treat pathogenic polyclonal B cell activation or switching taught by Kozin, including with humanized versions of said antibodies as taught by Hughes for human patients with autoimmune diseases, and including by the intravenous (iv) route of administration as taught for administration of T cells by Zeng *et al.*"

Appellants respectfully disagree with the conclusions of the Examiner, and submit that the art provides no reasonable expectation that CD1 is a causative factor in the development of immune

diseases as set forth in the claims; and if it is associated, there is no reasonable expectation that interfering with CD1 would be beneficial, rather than deleterious to the development of disease.

The present claims are directed to a method of treatment for autoimmune conditions such as lupus (SLE), by administration of antibodies that interfere with T cell recognition of CD1. Key to the invention is the demonstration provided by Appellants that *in vivo* blocking of CD1 by administration of antibodies significantly reduced the peak levels of serum IgG and IgG anti-dsDNA autoantibodies, and delayed disease progression. Importantly, these results were obtained with a spontaneous disease model representative of clinical disease.

The Examiner's position is that there was a reasonable certainty that administering anti-CD1 antibodies would treat such disease. The basis for this statement lies in drawing conclusions from several different pieces of art. Appellants would like to first review these conclusions, based on the statements made in the Examiner's Answer.

The Examiner's summary of the purported teachings of Amano *et al.* is as follows:

1. Interaction between anti-CD1 T cells and CD1 expressing B cells leads to mutual activation of both cell types. [1]
2. T cell proliferation of the CD1-restricted T cells in response to CD1-transfected B cells could be blocked by the use of the monoclonal antibody 3C11.[2]
3. Transgenic anti-CD1 T cells can induce SLE when transferred into nude host mice that do not spontaneously develop the disease.[3]
4. Transgenic T cells can activate wild-type BALB/c cells via the mechanism of cross-linking cell surface CD1 to secrete IgM and IgG *in vitro*.[4]
5. Spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice is mediated by the $CD1^{hi}$ subset of B cells.[5]

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[1] Examiner's Answer, page 9, line 14.
[2] Examiner's Answer, page 9, line 17.
[3] Examiner's Answer, page 9, line 18.
[4] Examiner's Answer, Page 9, line 21.
[5] Examiner's Answer, Page 10, lines 1-2.

Appellants respectfully submit that this summary of the reference fails to consider the unusual model system upon which the reference was based, and in failing to consider these circumstances, extrapolates beyond what is actually taught. It may be noted herein that a Declaration by Dr. Strober was provided during examination, to provide for an expert assessment of this reference.

The T cells that were studied by Amano *et al.* were not normal T cells. The paper was based on work with transgenic animals. These animals were genetically manipulated to carry a gene encoding a T cell receptor that binds to CD1. By introducing such a transgene, there is a significant and artificial shift in T cell populations, resulting in effects that cannot provide a reasonable expectation of the effect one might observe in spontaneous disease. In this model, the transgene was expressed in a majority of T cells in the animal. Because these coding sequences are artificially introduced, expression was not restricted to the NKT cell population, which is the population of cells that might react with CD1 in a normal situation. Rather, the transgene forced expression in conventional T cells, which do not normally recognize CD1. The transgenic cells used in this work are (a) artificially found at a very high concentration; (b) artificially expressing a receptor on a different class of cells and (c) artificially transferred into a host animal.

In reviewing the Examiner's summary points with respect to Amano *et al.*, Appellants submit that important information as to the teachings has been omitted, which information is important to the unobviousness of the present invention.

The Examiner point (1) is that *interaction between anti-CD1 T cells and CD1 expressing B cells leads to mutual activation of both cell types*, and point (2) is that *T cell proliferation of the CD1-restricted T cells in response to CD1-transfected B cells could be blocked by the use of the monoclonal antibody 3C11.*

In fact, what was demonstrated is that a T cell **clone** with an **invariant Vβ9/Vα4.4 rearrangement** proliferated in response to a B cell line **transfected with CD1 encoding sequences**. What these experiments show is that certain T cell clones, which are isolated and grown **in culture**, and which have a specific invariant rearrangement of the T cell receptor, are able to recognize CD1 as a stimulating antigen. It may also be noted that the antibody 3C11, which is reported to block the interaction, **failed** to demonstrate a significant expression of CD1 on B cells

from wild type mice[6]. The results of these experiments do not inform one of skill in the art as the interaction between T cells and B cells in a spontaneous *in vivo* disease context.

Point (3) is *that transgenic anti-CD1 T cells can induce SLE when transferred into nude host mice that do not spontaneously develop the disease.*

In fact, it was first shown the transgenic animals themselves, which have large numbers of transgenic T cells, **do not develop** any pathogenic polyclonal B cell activation. Further, while certain subpopulations of transgenic T cells cause disease, **other** populations of these transgenic T cells, which are more representative of native populations, **suppress** disease. The injection of the double negative cells, which correspond to the cells that originally expressed the transgene, were **protective of disease**, while the single positive cells, which do not correspond to the original cell type, **caused a disease** phenotype.

What these experiments show is that certain types of cells, if highly manipulated and taken out of context, can cause disease. One of skill in the art is therefore not informed as the interaction between T cells and B cells in a spontaneous *in vivo* disease context, and could reasonably expect that CD1 would be causative of spontaneous disease.

Point (4) is that *transgenic T cells can activate wild-type BALB/c cells via the mechanism of cross-linking cell surface CD1 to secrete IgM and IgG in vitro.*

This statement relates to experiments that were not provided by Amano *et al.* but were provided in a citation to the work of Zeng *et al.* (1998). The specific citation may be found in Amano *et al.* at page 1716, column 2, second paragraph. The actual data is represented in Zeng *et al.*, page 526, last paragraph to page 527.

The T cells referred to in these experiments are transgenic T cells. As discussed above, the transgene is expressed in cells that do not normally express this sequence. In the transgenic mouse, conventional T cells recognize CD1, while in normal animals and in spontaneous disease, conventional T cells do not recognize CD1.

What these experiments show is that certain types of cells, if highly manipulated and taken out of context, can cause antibody synthesis in a culture system. One of skill in the art is therefore not informed as the interaction between T cells and B cells in a spontaneous *in vivo* disease context.

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[6] Amano et al., page 1716, column 2, lines 10-12.

Indeed, when one looks at the *in vivo* relevance of this interaction, **none** of the transgenic mice developed **proteinuria** or **anti-ds DNA antibodies** (which are indicia of lupus) at a time point when animals that develop spontaneous disease have done so.

Point (5) is that *spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice is mediated by the CD1^{hi} subset of B cells.*

This statement relates to experiments that were not provided by Amano *et al.* but were provided in a citation to the work of Zeng *et al.*, in a manuscript that was not published prior to the filing of the priority document to the present application. The specific citation may be found in Amano *et al.* at page 1716, column 2, second paragraph. One cannot determine, based on this single sentence in the Amano *et al.* reference, if these spontaneously secreted antibodies related to disease, if the cells were actually involved in the disease process, if the spontaneous secretion was *in vivo* or *in vivo*, whether CD1 played a causative role in the secretion of antibody, and whether blocking CD1 would have an effect on the antibody secretion. In the absence of any corroborating data, or a showing that CD1 had an actual causative role in the development of disease, this statement can be nothing more than an invitation to experiment.

The next reference discussed by the Examiner is Kotzin *et al.*, which is stated to teach that pathogenic IgG autoantibody in lupus occurs by clonal expansion of somatically mutated anti-DNA antibody producing B cells. Appellants respectfully submit that Kotzin fails to teach an association of CD1 with the disease, and does not show the effectiveness of blocking CD1 to treat lupus-like disease. It has been believed for many years that lupus is caused by B cells and pathogenic antibody production, however this knowledge does not provide a mechanism for treatment of the disease.

The Examiner's summary of the purported teachings of Zeng *et al.*, "*Subsets of Transgenic T cells that recognize CD1 Induce or Prevent Murine Lupus: Role of Cytokines*" is as follows:

1. T cells with transgenic TCR that recognize CD1 on syngeneic B cells could induce lupus in nude mice.[7]

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[7] Examiner's Answer, page 10, lines 9-10.

2. T cells expressing the transgenic TCR specific for CD1 regardless of if they were double negative T cells or single positive T cells could induce or protect from disease.[8]
3. The cytokine secretion patterns of T cells plays a critical role in regulating B cell activation.[9]
4. Both single positive and double negative T cells from these mice augment the secretion of anti-ds DNA autoantibodies *in vitro*.[10]
5. Administration of anti-TCR antibodies (against Vα14) exacerbates the development of lupus.[11]
6. In NZB/NZW mice, a subset of T cells that recognize CD1 and secrete IL-4 are lost before the development of disease.[12]

In reviewing the Examiner's summary points with respect to Zeng *et al.*, Appellants submit that important information as to the teachings has been omitted, which information is important to the unobviousness of the present invention.

Point (1) is that *T cells with transgenic TCR that recognize CD1 on syngeneic B cells could induce lupus in nude mice*.

The T cells referred to in these experiments are transgenic T cells. As discussed above, the transgene is expressed in cells that do not normally express this sequence. In the transgenic mouse, conventional T cells recognize CD1, while in normal animals and in spontaneous disease, conventional T cells do not recognize CD1.

Further, the recipient animals were athymic (*i.e.* they lacked any T cells prior to injection of the transgenic T cells) and were given whole body irradiation at a dose of 800 cgy. This is a lethal dose of radiation, which eliminates substantially all of the immune cells in the animal. Therefore, the animal's immune system was reconstituted with the transfer of the transgenic bone marrow cells. It was subsequently found that, although the transgenic animals did not develop disease, the irradiated animals did.

Appellants respectfully submit that the highly artificial nature of this experiment: the lethally irradiated host animals; the transgenic conventional T cells having an unnatural phenotype; the

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[8] Examiner's Answer, page 10, lines 14-15.

[9] Examiner's Answer, page 10, lines 18-19.

[10] Examiner's Answer, page 10, lines 21-22.

[11] Examiner's Answer, page 11, line 3.

[12] Examiner's Answer, page 11, lines 4-7.

transfer of the cells into the host; in combination provide considerable doubt as the effect that these cells might have in a spontaneous disease situation.

Importantly, when cells from the double negative transgenic animal were transferred into these same recipients, they all **failed** to develop disease.[13] And, the injection of cells from euthymic double positive transgenic mice **failed** to induce disease.

The Examiner's point (2) speaks for itself. *T cells expressing the transgenic TCR specific for CD1 regardless of if they were double negative T cells or single positive T cells could induce or protect from disease.* It is clear that the association of CD1 with lupus was highly tenuous, as set forth in the cited prior art, and one of skill in the art could not be certain if cells interacting by CD1 were involved in disease; if such involvement was beneficial or deleterious; and whether blocking such interaction would have an effect, and if there was an effect, whether it would be beneficial or deleterious. As shown by Zeng *et al.* (page 529, second column), transgenic cells could just as readily prevent disease as cause it, and indeed, the very title of the article speaks to this ambiguity.[14]

The Examiner's point (3), *the cytokine secretion patterns of T cells plays a critical role in regulating B cell activation*, does not bear on the role of CD1 in spontaneous lupus. Appellants are not claiming the manipulation of cytokine secretion profiles for the treatment of lupus.

The Examiner's point (4), *both single positive and double negative T cells from these mice augment the secretion of anti-ds DNA autoantibodies in vitro*, is the same as point (4) with respect to Amano *et al.*, and is addressed above.

The Examiner's points (5 and 6) relate to some of the author's conclusions in the final paragraph of the Zeng *et al.* publication, which reads as follows:

> In addition, MRL/*gld/gld*, and NZB/NZW F_1 mice lose a subset of T cells ($NK1.1^+V\alpha14$) that recognizes CD1 and secretes high levels of IL-4 just before lupus develops. Anti- $V\alpha14$ monoclonal antibodies injected into MRL/*lpr* mice exacerbates the development of lupus, and depletes this T cell subset. The latter subset shows two characteristics (recognition of CD1 and high level secretion of IL-4) with the $CD4^-CD8^-$ T cell subset in the marrow that prevented lupus in this study.

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[13] Zeng et al., page 528, column 1, second paragraph.

[14] "*Subsets of Transgenic T cells that recognize CD1 Induce or Prevent Murine Lupus: Role of Cytokines*"

Appellants respectfully submit that these teachings, which the Examiner puts forth as evidence for the obviousness of the presently claimed invention, in fact, clearly teach away from the invention. The reference states that **depletion** of T cells that recognize CD1 **exacerbates** the development of lupus. The trait of CD1 recognition is shared by "the $CD4^{-}CD8^{-}$ T cell subset in the marrow that **prevented lupus** in this study".

Clearly, one of skill in the art could have no expectation that blocking CD1 would treat lupus in a spontaneous disease model. In a spontaneous disease, there is no simple segregation of T cells of one type or another. Given that these cells (within the confines of a highly artificial system) **induce or prevent** disease, one has no expectation of efficacy in treatment.

Although the art suggested a possible connection between spontaneous lupus and CD1, there was substantial uncertainty that CD1 had a causative role, or was merely associated with the disease in these systems, and if it was associated, whether it was beneficial or deleterious. Without the findings provided in the present application, one of skill in the art could not have a reasonable certainty of success practicing the claimed methods.

Appellants respectfully submit that the remaining references do not remedy the deficiencies of the primary references. Blumberg *et al.* teaches the expression of CD1 on B cells, monocytes and Langerhans cells, but fails to demonstrate the effectiveness of blocking CD1 to treat lupus-like disease.

Hughes provides background for the use of antibodies as therapeutics, but fails to teach the usefulness of antibodies specific for CD1 in the treatment of lupus-like disease.

With respect to Claim 13, Appellants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references. Prior to the *in vivo* demonstration of efficacy provided herein, there was substantial uncertainty as to the correlation between CD1 and lupus, particularly with respect to causality.

Appellants respectfully submit that the invention of Claim 13 is not made obvious by the cited combination of references. As discussed above, the prior art does not provide a reasonable expectation that administration of CD1 would be effective in treating lupus-like disease. The inclusion of a second therapeutic regimen is not relied upon for patentability, but is merely put forth as a variation on Appellants methods.

Based on the teachings of the prior art, one of ordinary skill in the art would not have a reasonable expectation of success for the presently claimed invention. Withdrawal of the rejection is requested.

Appellants respectfully request that the rejection of 1-2, 6-8, 10, 12 and 13 under 35 U.S.C. 103 be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

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